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# Subclinical Hypothyroidism

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**Abstract**

*Subclinical hypothyroidism (SCH) is a biochemical condition characterized by high serum thyroid stimulating hormone (TSH), with normal levels of thyroid hormones and without overt clinical features of hypothyroidism.*

*Thyroxine replacement therapy is reasonable for patients with a TSH greater than 10 mU/L because the rate of progression to overt hypothyroidism is up to 5% per year in comparison with lower TSH levels.*

*For patients with a mild degree of SCH (TSH ≤ 10 mU/L) thyroxine replacement therapy is recommended if they have symptoms, goiter, anti-TPO antibodies or infertility and in pregnant patients.*

*This review discusses the risks and/or benefits of thyroxine replacement treatment of subclinical hypothyroidism for those patients with a serum TSH level of 4.5-10.0 mIU/L.*

**Keywords:** *Subclinical hypothyroidism, Thyroid stimulating hormone, Cardiovascular risk, Cognition, Thyroxine replacement.*

## Introduction

Subclinical hypothyroidism (SCH) is characterized by a serum TSH above the upper reference limit in combination with a normal free thyroxine (T4).

The National Health and Nutrition Examination Survey (NHANES III) studied an unselected U.S. population over age 12 between 1988 and 1994, using the upper limit of normal for TSH as 4.5mIU/mL.[1] The prevalence of subclinical disease was 4.3% and of overt disease was 0.3%.

The Colorado thyroid disease prevalence survey, in which self-selected individuals attending a health fair were investigated and an upper normal TSH value of 5.0 mIU/L was used, reported a prevalence of 8.5% for subclinical, in people not taking thyroid hormone. [2]

Causes of subclinical hypothyroidism (SCH) include autoimmune thyroiditis, previous treatment for hyperthyroidism, infiltrative disease or infectious disorder of the thyroid gland, inadequate thyroid hormone supplementation of hypothyroid patients, previous thyroid surgery or history of external radiotherapy of the head and neck area. Several drugs, such as lithium carbonate, cytokines, and interferon, may induce subclinical or overt hypothyroidism. Serum TSH concentrations are higher in elderly and in obese individuals.

Few patients with SCH have typical hypothyroid symptoms. The Colorado Thyroid Disease Prevalence Study has shown that symptoms as dry skin, poor memory, slow thinking, tiredness, muscle cramps, cold intolerance, hoarse voice, and constipation are more in those with subclinical hypothyroidism compared to euthyroid ones. [3]

SCH has been associated with functional cardiac abnormalities. Vascular abnormalities, such as arterial stiffness, increased vascular resistance, endothelial dysfunction, and atherosclerosis, have been also described. [4]

Studies on the risks of cardiovascular disease and mortality due to coronary heart disease in these patients, however, have yielded conflicting results. To

date, the clinical importance of cardiovascular effects after long-term SCH has not been clearly defined. [4] The relationship between SCH and lipid metabolism is also not clear. [5]

SCH has been linked with variable increases in total cholesterol and LDL-cholesterol, higher plasma concentrations of oxidized LDL-cholesterol, and inconsistent changes in serum concentrations of HDL-cholesterol. [5]

SCH may also be associated with mood disorders such as major depression. Some studies have reported that higher TSH level is associated with a lower cognitive function, whereas others found that higher TSH is associated with better cognitive performance.

2-28% of patients with SCH progress to overt hypothyroidism, depending on baseline TSH concentration, age, gender, and the presence of anti-thyroid antibodies.

In a prospective follow up study, the rate of overt hypothyroidism was about 10% in all the study population, but was 2%, 20%, and 73% in patients with first TSH concentrations of 5.0-9.9 mU/L, 10.0-14.9 mU/L, and 15.0-19.9 mU/L, respectively. [6]

SCH can be divided into two categories, depending on the magnitude of the increase in serum TSH, with concentrations of 4.5-10 mU/L considered mild disease and TSH >10 mU/L considered a severe disease.

LT4 therapy is reasonable for patients with a TSH greater than 10 mU/L because the rate of progression to overt hypothyroidism is up to 5% per year in comparison with lower TSH levels.

Most expert groups have recommended LT4 therapy for patients with a mild degree of SCH (TSH ≤ 10 mU/L) if they have symptoms, goiter, anti-TPO antibodies or infertility and in pregnant patients. An elevated TSH in pregnant women should be treated with T4, as there is an association between high maternal TSH and adverse neuropsychological fetal outcomes

The following are studies supporting the benefit of treatment of mild subclinical hypothyroidism in non-pregnant adults.

## Symptoms of Hypothyroidism

In a randomized, double-blind, crossover study of L-thyroxine and placebo, one hundred patients with SCH [mean TSH 6.6 mIU/L without previously treated thyroid or vascular disease were studied. During the l-thyroxine treatment, there were significant improvements in some patient-reported outcomes. The proportion of patients reporting fatigue (ThySC questionnaire) was decreased from 89 to 78% during thyroxine therapy; P <0.006. Other hypothyroid symptoms showed a trend toward improvement but did not reach statistical significance. [7]

Although other studies have failed to show improvement in symptoms with L-thyroxine therapy, based on this study 2013 ETA Guideline have suggested giving a trail if tiredness is present. [8]

## Mood Disturbance /Mental Health

In a randomized double-blind placebo-controlled clinical trial, Sixty subjects with subclinical hypothyroidism (defined as serum TSH level between 4.5 mU/l and 10 mU/l in the presence of normal free-T4) were enrolled. The intervention and control groups received levothyroxine and placebo respectively for 3 months. Memory quotient was evaluated at the beginning of the study and three months after enrollment, using Wechsler's memory. The study showed the efficacy of levothyroxine for cognitive function of subjects with subclinical hypothyroidism. There was a significant improvement of mental control, logical memory, associate learning, and memory quotient. [9]

In a prospective, open-labeled nonrandomized interventional study,17 subclinical hypothyroidism, (mean TSH level was 6.1 mU/l) underwent neuropsychological tests at baseline and 3 and 6 months after LT4 replacement. Verbal, Spatial and Associative memory normalized when L –thyroxine was titrated to normalize TSH. [10]

The beneficial effects of L-thyroxine therapy on cognitive function seen in younger subclinical hypothyroidism patient not found in older age groups (>65 years). [11, 12]

In a placebo-controlled, double-blind intervention study with T4 medication for 1 yr. Sixty-nine of those with SHT were included (TSH of 3.5–10.0 mIU/liter). Cognitive functions were tested at baseline and after treatment with placebo or L-T4 for 12 months. There were no significant differences in cognitive function and hypothyroid symptoms between the two groups and T4 substitution had no effect on any of the parameters measured. [13]

## Dyslipidaemia

1200 participants were included in a cross-sectional population-based study on risk factors for cardiovascular diseases. The prevalence of SCH was 1.9% in men and 7.6% in women. An increase of 1 mU/l TSH was associated with an increase of 0.09 mmol/l in women and 0.16 mmol/l in men total plasma cholesterol (95% confidence interval (CI) 0.02-0.16 mmol/l). [14]

A meta-analysis showed that Thyroid replacement treatment in patients with hypercholesterolemia and SCH, restoring the TSH levels to normal, decreases total plasma cholesterol by 0.4 mmol/l, independently of the initial plasma level but plasma levels remain elevated in most patients. The effect of thyroid substitution therapy on HDL-cholesterol was not consistent. [15]

49 subclinical hypothyroidism patients (TSH level was <10 mU/l in 92% of patients) were randomly assigned to levothyroxine therapy or placebo and re-evaluated after 6 months of euthyroidism. Levothyroxine treatment resulted in a significant decrease of both TC and LDL-C concentrations (P = 0.003). [16]

In a randomized, double-blind, cross-over study, including 100 patients with stable subclinical hypothyroidism [mean TSH 6.6 mIU/liter], 100 μg L -thyroxine or placebo daily for 12 wk each. L -thyroxine treatment significantly reduced serum TC, low-density lipoprotein cholesterol, and waist to hip ratio. [7]

## Cardiovascular System, Heart Failure, and Ischaemic Heart Disease

A large meta-analysis of 15 observational studies included 2,531 subclinical hypothyroidism participants(with mild subclinical hypothyroidism (TSH levels <10 mIU/liter)) and 26,491 euthyroid individuals, showed that IHD incidence and prevalence were higher in subclinical hypothyroidism subjects compared with euthyroid participants from studies including those younger than 65 yr, but not studies of subjects aged older than 65 yr. Cardiovascular/ all-cause mortality was also elevated in participants from the younger than 65-yr studies, but not from the studies of older people. [17]

A cross-sectional study of a general population showed that cardiovascular disease was more frequent in males younger than 50 years of age with SCH compared to euthyroid males. [18]

Increased CHD events were found over 10 years of follow up in subclinical hypothyroidism men with mean age of 58.5 years and serum TSH <10 mU/l,[19] and over 20 years of follow-up in a similar mixed-gender cohort. [20]

Most of the above data did not show the benefit of treatment of mild SCH in elderly patients.

The decision to treat elderly people is still an unresolved clinical challenge, first, due to a lack of appropriately powered randomized controlled trials of L-T4 in SHT patients, examining cardiovascular hard endpoints in various classes of age; and second, because of the negative effects of possible overtreatment. [21]

The arguments against treatment are its expense and the likelihood that some patients will not benefit. There is also a danger of over-treatment, which could cause iatrogenic hyperthyroidism. Subclinical hyperthyroidism has been associated with negative outcomes including osteopenia and atrial fibrillation[22]

## Conflicts of interest

There are no conflicts of interest.

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